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ORIGINAL ARTICLE

Positive Impact of the Bionic Pancreas on Diabetes Control in Youth 6–17 Years Old with Type 1 Diabetes: A Multicenter Randomized Trial

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Abstract

Objective: To evaluate the insulin-only configuration of the iLet® bionic pancreas (BP) in youth 6–17 years old with type 1 diabetes (T1D).

Research Design and Methods: In this multicenter, randomized, controlled trial, 165 youth with T1D (6–17 years old; baseline HbA1c 5.8%–12.2%; 35% using multiple daily injections, 36% using an insulin pump without automation, 4% using an insulin pump with low glucose suspend, and 25% using a hybrid closed-loop system before the study) were randomly assigned 2:1 to use BP ($n=112$) with insulin aspart or insulin lispro (BP group) or to a control group ($n=53$) using their personal standard care insulin delivery (SC group) plus real-time continuous glucose monitoring (CGM). The primary outcome was HbA1c at 13 weeks.

Results: Mean HbA1c decreased from 8.1% ± 1.2% at baseline to 7.5% ± 0.7% at 13 weeks with BP versus 7.8% ± 1.1% at both baseline and 13 weeks with SC (adjusted difference = –0.5%, 95% CI –0.7% to –0.2%,

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$P < 0.001$). Participants with baseline HbA1c ≥9.0% ($n = 34$) decreased mean HbA1c from 9.7% ± 0.8% to 7.9% ± 0.6% after 13 weeks with BP compared with 9.7% ± 0.5% to 9.8% ± 0.8% with SC. Over 13 weeks, mean time in range (TIR) 70–180 mg/dL increased by 10% (2.4 h per day) and mean CGM glucose was reduced by 15 mg/dL with BP compared with SC ($P < 0.001$). Analyses of time >180 mg/dL, time >250 mg/dL, and standard deviation of CGM glucose favored BP ($P < 0.001$). Time <54 mg/dL was low at baseline (median 0.2%) and not significantly different between groups over 13 weeks ($P = 0.24$). A severe hypoglycemia event occurred in 3 (2.7%) participants in the BP group and in 1 (1.9%) in the SC group.

Conclusions: In youth 6–17 years old with T1D, use of insulin-only configuration of BP improved HbA1c, TIR, and hyperglycemic metrics without increasing CGM-measured hypoglycemia compared with standard of care. Improvement in glycemic metrics was most pronounced in participants with high baseline HbA1c levels.

Clinical Trial Registry: clinicaltrials.gov; NCT04200313.

Keywords: Artificial pancreas, Bionic pancreas, Evaluation, Automated insulin delivery, Pediatrics, Type 1 diabetes.

Introduction

Children and adolescents have the highest mean HbA1c levels of all people living with type 1 diabetes (T1D), with recent T1D Exchange Registry data indicating only 17% of youth achieving the American Diabetes Association goal of HbA1c <7%.[1,2] Reports indicate that the average HbA1c in youth is gradually increasing over time, a disturbing finding that heightens the impetus to find reasonable strategies to improve glycemic control.[2–4]

Automated insulin delivery (AID) systems have the potential to increase the number of children and adolescents with T1D who meet goals for therapy.[5] Currently available AID systems include hybrid closed-loop (HCL) systems that automate basal insulin delivery, and in some cases, automate delivery of partial correction boluses. All current systems require determination of basal rate profiles, insulin correction factors, and carbohydrate ratios by a health care provider (HCP), as well as carbohydrate counting and delivery of meal boluses based on entered carbohydrates by the user.

In pivotal trials resulting in approval or clearance by the Food and Drug Administration (FDA), the Medtronic Minimed™ 670G, the Tandem t:slim X2 with Control-IQ® Technology (Control-IQ), and the Insulet Omnipod® 5 were considered to be safe with improved glucose outcomes compared with baseline levels in children ages 6–17.[6–9] In case of the Control-IQ system, glucose outcomes measured with continuous glucose monitoring (CGM) were shown to be superior to those of a control group using sensor-augmented pump therapy in a randomized trial.

Newer AID systems are advancing paradigms of automation beyond traditional HCL, by reducing the need for user interaction, both at device initialization and in daily use. The iLet bionic pancreas ([BP]; Beta Bionics) is an AID system initialized only with body weight, without requiring the input of any information about previous insulin dosing. All insulin doses are determined autonomously by BP insulin-dosing algorithms, which determine and continually adapt basal insulin doses, correction insulin doses, and meal-announcement doses to meet the individual's insulin needs in response to the CGM input signal to BP. Insulin doses cannot be modified by the user or HCP. Meals and large snacks are announced by the user without carbohydrate counting as ''Usual For Me,'' ''More'' (approximately 50% more than usual), or ''Less'' (approximately 50% less than usual) compared to other meals of the same type (i.e., ''Breakfast,'' ''Lunch,'' and ''Dinner'').

In response to qualitative meal announcements, the system delivers ~75% of the autonomously estimated insulin need immediately, and then will autonomously add or refrain from additional basal or correction insulin dosing postprandially, as necessary. When CGM data are not available, BP continue to make all insulin dosing decisions autonomously, based on a basal insulin profile determined, continually updated, and stored by BP when CGM data were available, and in response to any entered blood glucose (BG) values obtained from a capillary glucometer. The BP have been developed both as an insulin-only system as well as a bihormonal system that doses both insulin and glucagon.

We conducted a multicenter randomized trial of adults and youth ≥6 years old with T1D to evaluate the efficacy and safety of the insulin-only configuration of BP, using insulin aspart or insulin lispro. The control group continued their prestudy subcutaneous insulin delivery (multiple daily injections [MDI], an insulin pump without automation of insulin delivery, an insulin pump with a predictive low glucose suspend feature, or an insulin pump as part of an HCL system) in conjunction with real-time (unblinded) CGM. Herein we report the results of the trial in youth 6–17 years old.

Methods

This parallel group multicenter randomized trial enrolled adults and youth ≥6 years old with T1D.[10] The pediatric cohort (6–17 years old) was enrolled at 10 pediatric diabetes centers in the United States. The protocol was approved by a central institutional review board. Informed consent was obtained from participants' legal authorized representative and assent was obtained from participants >7 years old. An investigational device exemption for the conduct of the trial was approved by the US FDA. The full protocol is available at https://www.jaeb.org/finaliobp and key aspects are summarized herein.

To be eligible for the trial, participants had to have T1D treated with insulin for at least 1 year by MDI or pump therapy with or without CGM or HCL. There was no restriction on HbA1c level and no exclusion for prior severe hypoglycemia events or prior diabetic ketoacidosis events. A complete list of inclusion and exclusion criteria is available

at clinicaltrials.gov (NCT04200313). To enroll participants with characteristics as similar as possible to the general population of people with T1D, recruitment targets included having half of the participants be 6–11 years of age and half be 12–17 years of age, with at least 33% of MDI users, at least 33% with HbA1c ≥8.0%, and no more than 20% with HbA1c <7.0%.

Participants using a personal Dexcom G6 CGM System (Dexcom, Inc.), who had ≥85% of possible glucose data during the 14 days before the screening visit, could proceed directly to randomization once eligibility was confirmed. All other participants completed a 14-day baseline data collection period using a study-provided Dexcom G6 CGM and were required to have at least 85% of CGM values during the 14 days before proceeding to randomization. Participants using a personal Dexcom G5 or G6 sensor before enrollment used an unblinded G6 sensor, while all others wore a blinded G6 sensor. If participants used a non-Dexcom CGM, they were encouraged to continue its use during the baseline data collection period (while wearing the blinded Dexcom CGM).

Randomization was performed on the study website using a computer-generated sequence with a permuted block design, stratified by site. Participants were randomly assigned in a 2:1 ratio to use of BP with insulin lispro or insulin aspart (BP group), or standard-of-care insulin delivery plus use of a real-time Dexcom G6 CGM (SC group).

Participants assigned to the BP group were provided with the iLet pump that is part of the BP system, Dexcom G6 sensors and transmitters, insulin infusion sets (Inset I, Unomedical), a Contour®Next One Blood Glucose Monitoring System (Ascensia Diabetes Care, Basel, CH) and test strips, and a Precision Xtra ketone meter (Abbott Diabetes Care) and test strips. Participants filled 1.6-mL glass, ready-to-fill cartridges with their personal insulin aspart or lispro if used from vials; if they used pens or a different insulin, the study provided them with insulin aspart or insulin lispro in 10-mL vials. Participants were trained on the use of the BP system and given specific written and video instructions for identifying and managing possible infusion set failures, which included a ''ketone action plan'' if instances of prolonged hyperglycemia arose. BP use was initiated during this training session. There were no restrictions on diet or exercise during the trial period.

The algorithms were initialized only by entering the participant's body weight; there was no run-in or warm-up period for the device before automation of insulin delivery commenced. The default glucose target of ''Usual'' (120 mg/dL, 6.7 mmol/L) could be shifted by ±10 mg/dL (0.56 mmol/L), down to ''Lower'' or up to ''Higher''; a different target from the default target could be set for part of the day.

Participants assigned to the SC group continued to use their prestudy personal insulin delivery method and insulin regimen, which for some included an FDA-approved/cleared HCL system. All participants used an unblinded real-time Dexcom G6 CGM for daily glucose monitoring, with study-provided sensors and transmitters. If they previously used a different CGM system, they could continue its use in addition to the Dexcom G6, at their discretion. CGM-naive participants in the SC group were trained in the insertion and maintenance of the Dexcom G6 CGM and in the interpretation and use of CGM data.

Participants in the SC group were not provided with a BG meter or ketone meter and were not provided with the ketone action plan given to the BP group. Diabetes management for participants in the SC group, including any adjustment to their insulin regimen and management of problems such as infusion set failures, was continued by their own diabetes care providers, not study staff.

After randomization, participants in both groups had phone contacts after 1–2 days and 1 week and had follow-up visits at 2, 6, 10, and 13 weeks. Some visits were completed remotely through video conference due to the COVID-19 pandemic. Data from BP were downloaded at weeks 6 and 13 when these were in-person, or when BP were shipped back to the study site whenever the week-13 visit was done by video conference. Blood samples from venipuncture or fingerstick[11] were collected at randomization and after 6 and 13 weeks for measurement of HbA1c by a central laboratory at the University of Minnesota Advanced Research and Diagnostic Laboratory (measured with a Tosoh BioScience instrument).

Participants completed a questionnaire weekly, with each day of the week sampled equally throughout the trial, which queried them about episodes of hypoglycemia and treatment of such events with carbohydrate during the prior 24 h. Quality-of-life questionnaires were completed at baseline and during follow-up; results from the questionnaires will be reported separately.

Reporting of adverse events was solicited throughout the trial. Severe hypoglycemia was defined as hypoglycemia requiring assistance because of altered consciousness. Diabetic ketoacidosis was defined by the criteria established by the Diabetes Control and Complications Trial.[12]

Statistical methods

Change in HbA1c was the primary outcome and CGM metrics were secondary outcomes. The study was planned to include ~110 participants 6–17 years old in the BP group and 55 in the SC group.

Statistical analyses were performed on an intention-to-treat basis. Continuous outcomes were compared between groups using linear mixed-effects regression models and binary outcomes with logistic regression models, adjusting for the baseline value of the metric, age, and site (random effect). Modification of the treatment effect by baseline variables was assessed by including an interaction term in the models described above. For key safety outcomes, when at least five events occurred combined between groups, treatment group comparisons were made using a Poisson regression model adjusting for age and HbA1c at randomization and site (random effect).

All analyses were prespecified, except for the treatment group comparisons in the subgroup with baseline HbA1c ≥9.0%, the subgroup using an HCL system before the study, and treatment group comparisons for the variance of HbA1c, mean glucose, and time in range (TIR) 70–180 mg/dL. Across all outcomes, the type I error was controlled with the use of the adaptive Benjamini-Hochberg false discovery rate correction procedure.[13]

Descriptive statistics include means with standard deviations (SDs) and medians with interquartile ranges (IQRs), depending on the distribution of data. All *P* values are two tailed, except as noted. Analyses were performed with SAS software, version 9.4 (SAS Institute).

Table 1. Participant Characteristics by Treatment Group

	BP (n = *112*)	*SC* (n = *53*)
Age (years)		
Mean ± SD	12 ± 3	12 ± 3
6 to <12, *n* (%)	47 (42)	23 (43)
12 to <18, *n* (%)	65 (58)	30 (57)
Range	6–17	6–17
Diabetes duration (years)		
Mean ± SD	6 ± 4	7 ± 4
Range	1–15	1–16
HbA1c level at randomization (%)		
Mean ± SD	8.1 ± 1.2	7.8 ± 1.1
≤7.0%, *n* (%)	18 (16)	12 (23)
7.1–7.9%, *n* (%)	34 (30)	19 (36)
8.0–8.9%, *n* (%)	33 (29)	15 (28)
≥9.0%, *n* (%)	27 (24)	7 (13)
Range	6.1–12.2	5.8–10.6
Sex—Female, *n* (%)	55 (49)	15 (28)
Race/Ethnicity group, *n* (%)		
White non-Hispanic	72 (64)	36 (68)
Black non-Hispanic	13 (12)	3 (6)
Hispanic or Latino	16 (14)	8 (15)
Asian	2 (2)	2 (4)
American Indian/Alaskan Native	1 (<1)	0 (0)
More than one race	6 (5)	4 (8)
Unknown	2 (2)	0 (0)
Annual household income, *n* (%)		
<$25,000	3 (3)	1 (2)
$25,000–<$35,000	4 (4)	1 (2)
$35,000–<$50,000	7 (6)	2 (4)
$50,000–<$75,000	8 (7)	5 (9)
$75,000–<$100,000	18 (16)	8 (15)
$100,000–<$200,000	35 (31)	17 (32)
≥$200,000	31 (28)	11 (21)
Unknown	6 (5)	8 (15)
Education,[a] *n* (%)		
<Bachelor's	37 (33)	16 (30)
Bachelor's	36 (32)	17 (32)
>Bachelor's	38 (34)	18 (34)
Unknown	1 (<1)	2 (4)
Health insurance, *n* (%)		
Private	90 (80)	40 (75)
Medicare/Medicaid	16 (14)	8 (15)
Other Government Insurance	6 (5)	4 (8)
None	0 (0)	0 (0)
Unknown	0 (0)	1 (2)
BMI		
Percentile[b] (%), mean ± SD	74% ± 24%	66% ± 27%
<5th percentile, *n* (%)	0 (0)	2 (4)
5th to <85th percentile, *n* (%)	64 (57)	37 (70)
85th to <95th percentile, *n* (%)	26 (23)	8 (15)
≥95th percentile, *n* (%)	22 (20)	6 (11)
Insulin/CGM device use, *n* (%)		
MDI without CGM	7 (6)	0 (0)
MDI with CGM	30 (27)	21 (40)
Pump without CGM	0 (0)	1 (2)
Pump with CGM (without automation)	45 (40)	13 (25)
Pump with predictive low glucose suspend	3 (3)	3 (6)
HCL system	27 (24)	15 (28)
Currently using CGM, *n* (%)	105 (94)	52 (98)
c-Peptide (ng/mL)[b]		
Mean ± SD	0.039 ± 0.115	0.042 ± 0.098
<0.007, *n* (%)	77 (79)	34 (72)
Total daily insulin (U/kg/day), median (IQR)	0.90 (0.75, 1.14)	0.87 (0.70, 1.10)
Time since most recent SH event,[c] *n* (%)		
Never had an event	93 (83)	40 (75)
<3 months ago	1 (<1)	0 (0)
3 to <6 months ago	1 (<1)	1 (2)
≥6 months ago	17 (15)	12 (23)
Time since last DKA event, *n* (%)		
Never had an event	65 (58)	29 (55)
<3 months ago	0 (0)	1 (2)
3 to <6 months ago	1 (<1)	0 (0)
≥6 months ago	46 (41)	23 (43)
Non-insulin blood sugar control medications taken, *n* (%)		
Metformin	1 (<1)	0 (0)

[a]Highest education level of parent or guardian.
[b]c-Peptide at randomization missing for 15 BP participants and 6 SC participants.
[c]A severe hypoglycemic event is defined as a hypoglycemic event that (1) required assistance of another person due to altered consciousness and (2) required another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

BMI, body mass index; BP, bionic pancreas; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HCL, hybrid closed loop; IQR, interquartile range; SC, standard care; SD, standard deviation; SH, severe hypoglycemia.

Results

There were 165 participants 6–17 years old included in the analyses: 112 randomly assigned to the BP group and 53 to the SC group. Mean age was 12 ± 3 years, with 42% being female. Racial/ethnicity distribution was 65% non-Hispanic White, 10% non-Hispanic Black, 15% Hispanic/Latino, and 9% other or more than one race (Table 1). Baseline HbA1c ranged from 5.8% to 12.2% (mean 8.0% ± 1.2%). At study entry, 95% were using CGM; insulin delivery was administered by MDI in 35%, by pump without automation in 36%, by pump with predictive low glucose suspend in 4%, and by an HCL system in 25%. Characteristics according to treatment group are shown in Table 1.

The trial was completed by 100% of participants in each group (Supplementary Fig. S1), and the overall visit and phone contact completion rate was 99% in each group. The BP were discontinued before the 13th week in five participants, all of whom remained in the trial (two due to frequent drops in glucose levels—both 6 years old with similar CGM-measured time <54 mg/dL at baseline and during use of BP, one due to frequent hyperglycemia, and two following self-harm attempts—one of which involved deliberate overdosing of insulin from BP by repeatedly announcing meals).

The BP were autonomously dosing insulin a median of 96% (IQR 93%–98%) of the time during the 13 weeks, with CGM input available for 88% (IQR 83%–92%) of the time. While BP were in use, median autonomous dosing was 96% (IQR 94%–98%) (Supplementary Table S1). In the SC group, CGM use was very high, with median usage over the 13 weeks of the trial being 94% (IQR 88%–97%).

Efficacy outcomes

Mean HbA1c decreased from 8.1% ± 1.2% at baseline to 7.7% ± 0.7% at 6 weeks, and 7.5% ± 0.7% at 13 weeks in the BP group and was unchanged at 7.8% ± 1.1% at baseline, 6 weeks, and 13 weeks in the SC group (adjusted difference in mean change in HbA1c from baseline to 13 weeks = –0.5%, 95% CI –0.7% to –0.2%, $P < 0.001$, Table 2, Supplementary Fig. S2). Fifty-one percent of the BP group versus 8% of the SC group improved by >0.5% ($P < 0.001$) and 29% versus 6% improved by >1.0% ($P = 0.02$, Table 3).

The treatment effect on HbA1c was particularly large for participants with baseline HbA1c ≥9.0% (Table 4, Fig. 1), in whom mean HbA1c decreased from 9.7% ± 0.8% at baseline to 7.9% ± 0.6% at 13 weeks with BP compared with 9.7% ± 0.5% to 9.8% ± 0.8% with SC.

Improvements in mean TIR and mean CGM glucose were seen during the first day of BP use and remained relatively stable from the first week through the 13 weeks (Fig. 2, Supplementary Table S2). Over 13 weeks, mean TIR was increased by 10% (2.4 h per day) and mean CGM glucose was reduced by 15 mg/dL on average in the BP group compared with the SC group ($P < 0.001$) (Table 2, Supplementary Figs. S3–S5). Statistically significant differences favoring the BP group also were present for time >180 mg/dL, time >250 mg/dL, and mean glucose SD (Table 2), with the beneficial effect appearing to be greater overnight than during daytime. Over the 24 h of the day, the largest treatment group difference in CGM mean glucose was between 6 a.m. and 7 a.m. (Fig. 3).

Additional HbA1c and CGM outcomes reflective of hyperglycemia all indicated a strong treatment benefit for BP compared with SC (Table 3, Supplementary Tables S3). In addition to the improvement in the mean of the key metrics, the between participant variances for HbA1c, mean CGM glucose, and mean TIR were substantially smaller with BP compared with SC ($P < 0.001$, Supplementary Table S4, Fig. 4).

The amount of hypoglycemia was low in both groups at baseline and during the 13 weeks of trial through both day and night. Median time <54 mg/dL was 0.20% at baseline and 0.33% during the 13 weeks of trial in the BP group and 0.22% at baseline and 0.37% during follow-up in the SC group (adjusted difference = –0.04% [95% CI –0.13% to 0.03%], $P = 0.24$) (Table 2, Supplementary Fig. S6). The frequency of hypoglycemia reported during the 24 h before completion of each weekly questionnaire was similar in the two groups (Supplementary Table S5). Although there was no significant change in time in hypoglycemia for the cohort as a whole, some individual participants in the BP group who had high percentages of time <54 mg/dL at baseline experienced large reductions in hypoglycemia during 13 weeks on BP (Supplementary Fig. S6).

An analysis restricted to participants with baseline HbA1c >7.0% (Supplementary Table S6) demonstrated a larger treatment effect on HbA1c than the overall analysis, with an adjusted mean treatment group difference of –0.7% (95% CI –0.9% to –0.4%, $P < 0.001$), whereas an analysis restricted to participants not using an HCL system prestudy had an HbA1c difference similar to the overall analysis (mean treatment group difference –0.5%, 95% CI –0.8 to –0.3%, $P < 0.001$, Supplementary Table S7). Among the subgroup of 42 participants using an HCL system prestudy (which was continued during the study for the 15 in the SC group), there was no significant treatment group difference in HbA1c (Supplementary Table S8).

In subgroup analyses, the HbA1c and TIR benefits of BP compared with SC were evident across participant age range, for both higher and lower parent education level and family income level, and for both MDI and pump (without automation) users. In addition to a greater treatment effect on HbA1c observed with higher baseline HbA1c, the treatment effect on HbA1c also was greater with lower baseline TIR, higher baseline mean CGM glucose, and higher baseline time in hyperglycemia (Supplementary Tables S9 and S10).

Mean total daily dose (TDD) of insulin was not significantly different between the BP group and the SC group (Supplementary Table S11). Nominally, participants with baseline HbA1c ≥8.0% appeared to have a higher mean TDD of insulin than those with lower baseline HbA1c for both the BP and SC groups (Supplementary Tables S11 and S12), but with use of BP, change in TDD of insulin for these participants did not vary with change in HbA1c from baseline ($r = 0.08$). There was no significant treatment group difference in change in body weight, or body mass index (Supplementary Table S13).

Adverse events and device issues

There were three severe hypoglycemia events in three participants in the BP group (2.7% of 112 participants) and one event in one participant in the SC group (1.9% of 53 participants). There was no case of diabetic ketoacidosis. Among the other reportable adverse events in the BP groups, most were related to hyperglycemia with or without ketosis and were attributable to infusion set failure (Table 5). Two participants were prescribed insulin glargine to use with BP due to prolonged periods of hyperglycemia (Supplementary Table S14). A summary of BP group devices issues is provided in Supplementary Table S15.

Discussion

This randomized controlled trial of the insulin-only configuration of BP in children 6–17 years of age with T1D demonstrated a statistically significant and clinically meaningful 0.5% reduction in HbA1c compared with standard of care, which included real-time CGM for all participants. CGM-measured hypoglycemia was low at baseline and remained low over the 13 weeks of trial.

There was also a statistically significant 10% increase in mean TIR, which equates with an average of 2.4 h per day greater TIR, and a statistically significant 15 mg/dL decrease in mean CGM glucose, as well as statistically significant decreases in hyperglycemia. This increase in TIR and decrease in mean CGM glucose were seen within 1 day of the

Table 2. Key Efficacy Outcomes

	Baseline		*Follow-up (at or over 13 weeks)*		*Adjusted difference BP minus SC (95% CI)*[b]	P[b]
	BP group (n = 112)[a]	*SC group (n = 53)*[a]	*BP group (n = 112)*[a]	*SC group (n = 53)*[a]		
Overall						
HbA1c (%), mean ± SD	8.1 ± 1.2	7.8 ± 1.1	7.5 ± 0.7	7.8 ± 1.1	−0.5 (−0.7 to −0.2)	<0.001
Mean glucose (mg/dL), mean ± SD	195 ± 39	195 ± 42	172 ± 14	187 ± 34	−15 (−21 to −9)	<0.001
Time 70–180 mg/dL, mean ± SD	47% ± 17%	48% ± 19%	60% ± 8%	50% ± 16%	10% (7% to 13%)	<0.001
Time >180 mg/dL, mean ± SD	51% ± 19%	50% ± 20%	38% ± 8%	47% ± 17%	−9% (−12% to −6%)	<0.001
Time >250 mg/dL, median (IQR)	20.6% (12.3%, 33.5%)	20.8% (10.7%, 34.4%)	11.8% (8.6%, 15.6%)	20.4% (11.3%, 27.3%)	−6.2% (−8.7% to −3.7%)	<0.001
Time <70 mg/dL, median (IQR)	1.3% (0.5%, 2.8%)	1.5% (0.4%, 2.9%)	1.8% (0.9%, 3.0%)	2.3% (1.2%, 3.1%)	−0.3% (−0.6% to 0.0%)	0.07
Time <54 mg/dL, median (IQR)	0.20% (0.03%, 0.59%)	0.22% (0.03%, 0.46%)	0.33% (0.18%, 0.63%)	0.37% (0.16%, 0.66%)	−0.04% (−0.13% to 0.03%)	0.24
SD (mg/dL), mean ± SD	72 ± 14	72 ± 17	66 ± 11	73 ± 15	−7 (−10 to −4)	<0.001
Coefficient of variation (%), mean ± SD	37% ± 6%	37% ± 7%	38% ± 4%	39% ± 5%	−0.8% (−1.9% to 0.3%)	0.15
Daytime (06:00–23:59)						
Mean glucose (mg/dL), mean ± SD	197 ± 39	197 ± 43	176 ± 15	189 ± 35		
Time 70–180 mg/dL, mean ± SD	46% ± 17%	46% ± 19%	57% ± 8%	49% ± 16%		
Time >180 mg/dL, mean ± SD	52% ± 19%	51% ± 20%	41% ± 8%	48% ± 17%		
Time >250 mg/dL, median (IQR)	22.2% (12.1%, 37.5%)	21.5% (10.5%, 34.1%)	13.7% (10.0%, 18.6%)	18.5% (10.4%, 30.4%)		
Time <70 mg/dL, median (IQR)	1.3% (0.5%, 3.2%)	1.3% (0.4%, 3.2%)	1.8% (1.0%, 2.9%)	2.1% (1.0%, 3.4%)		
Time <54 mg/dL, median (IQR)	0.21% (0.02%, 0.61%)	0.17% (0.00%, 0.44%)	0.34% (0.16%, 0.60%)	0.32% (0.15%, 0.61%)		
SD (mg/dL), mean ± SD	73 ± 15	72 ± 17	68 ± 10	73 ± 15		
Coefficient of variation (%), mean ± SD	38% ± 6%	37% ± 7%	39% ± 4%	39% ± 5%		
Nighttime (00:00–05:59)						
Mean glucose (mg/dL), mean ± SD	190 ± 43	189 ± 46	161 ± 18	182 ± 34		
Time 70–180 mg/dL, mean ± SD	49% ± 21%	52% ± 23%	68% ± 12%	53% ± 18%		
Time >180 mg/dL, mean ± SD	49% ± 22%	45% ± 24%	30% ± 12%	44% ± 19%		
Time >250 mg/dL, median (IQR)	16.7% (7.6%, 26.7%)	16.6% (6.8%, 33.8%)	6.0% (3.3%, 9.4%)	17.1% (9.8%, 26.4%)		
Time <70 mg/dL, median (IQR)	0.6% (0.0%, 2.8%)	1.0% (0.0%, 3.7%)	1.6% (0.7%, 2.6%)	1.9% (1.0%, 3.6%)		
Time <54 mg/dL, median (IQR)	0.00% (0.00%, 0.59%)	0.00% (0.00%, 0.82%)	0.27% (0.10%, 0.67%)	0.35% (0.12%, 0.61%)		
SD (mg/dL), mean ± SD	65 ± 17	66 ± 19	56 ± 14	69 ± 16		
Coefficient of variation (%), mean ± SD	35% ± 8%	35% ± 8%	35% ± 6%	38% ± 6%		

[a]Two BP participants and two SC participants missing 13-week HbA1c. Median amount of CGM data for analyses was 322 (IQR 310–336) hours at baseline and 1969 (IQR 1887–2040) during follow-up in the BP group and 325 (IQR 309–336) and 2045 (IQR 1917–2107), respectively, in the SC group.

[b]All statistical testing is for superiority. *P*-values and 95% CIs are from mixed-effect models adjusting for baseline value of the metric, age at randomization, and site (random effect). Missing data were handled using direct likelihood analyses. Due to a skewed distribution, % time >250, <70, and <54 mg/dL were transformed using a rank normal transformation. Multiple comparisons were adjusted using the Benjamini-Hochberg adaptive false discovery rate correction procedure.

CI, confidence interval.

Table 3. Additional Efficacy Binary Outcomes

	Follow-up (at or over 13 weeks)		*Adjusted difference BP minus SC (95% CI)*[b]	P[b]
	BP (n = *112*)[a] n *(%)*	*SC* (n = *53*)[a] n *(%)*		
HbA1c <7.0%	22 (20)	12 (24)	3% (−8% to 17%)	0.68
HbA1c <7.5%	52 (47)	17 (33)	20% (11% to 28%)	<0.001
HbA1c <8.0%	85 (77)	32 (63)	20% (9% to 30%)	0.002
HbA1c >9.0%	1 (1)	7 (14)	−17% (−27% to 15%)	0.09
HbA1c improvement from baseline >0.5%	56 (51)	4 (8)	37% (26% to 49%)	<0.001
HbA1c improvement from baseline >1.0%	32 (29)	3 (6)	16% (3% to 24%)	0.02
HbA1c relative improvement from baseline >10%	40 (36)	3 (6)	24% (10% to 37%)	0.003
HbA1c improvement from baseline >1.0% or HbA1c <7.0%	50 (45)	14 (27)	18% (3% to 34%)	0.02
Time 70–180 mg/dL >70%	6 (5)	6 (11)	−3% (−13% to 8%)	0.61
Time 70–180 mg/dL improvement from baseline ≥5%	81 (72)	27 (51)	19% (2% to 38%)	0.03
Time 70–180 mg/dL improvement from baseline ≥10%	74 (66)	19 (36)	29% (9% to 48%)	0.007
Time <70 mg/dL <4%	101 (90)	43 (81)	10% (4% to 16%)	0.004
Time <54 mg/dL <1%	98 (88)	44 (83)	7% (−2% to 16%)	0.15
Mean glucose <154 mg/dL and time <54 mg/dL <1%	4 (4)	5 (9)	−3% (−10% to 4%)	0.38
Time 70–180 mg/dL >70% and time <54 mg/dL <1%	6 (5)	4 (8)	0% (−9% to 10%)	0.90
HbA1c <7.0% for participants with baseline HbA1c >7.5%	*n* = 71 6 (8)	*n* = 30 1 (3)	8% (−14% to 31%)	0.34
Improvement in HbA1c > 0.5% without an increase in time <54 mg/dL by >0.5% or improvement in time <54 mg/dL by >0.5% without an increase in HbA1c by >0.5%	56 (51)	4 (8)	37% (28% to 45%)	<0.001
Improvement in time 70–180 mg/dL by >10% without an increase in time <54 mg/dL by >0.5% OR improvement in time <54 mg/dL by >0.5% without a decrease in time 70–180 mg/dL by >10%	64 (57)	12 (23)	33% (17% to 47%)	<0.001

[a]Two BP participants and two SC participants missing 13-week HbA1c.
[b]*P*-values are from a logistic regression model adjusting for the baseline value of the metric, age at randomization, and site (random effect). A 95% CI for the treatment group adjusted risk difference (BP minus SC) was produced using parametric bootstrapping. Multiple comparisons were adjusted using the Benjamini-Hochberg adaptive false discovery rate correction procedure.

initiation of BP use and remained relatively constant through the 13 weeks. Beneficial effects were seen during both daytime and nighttime. The improvement in glycemic metrics occurred without an increase in the TDD of insulin.

These glycemic results are noteworthy, considering that BP users (and their caregivers) did not count carbohydrates, set, or adjust basal insulin, or administer hyperglycemia correction boluses, while using the system. BP users provided qualitative estimates of carbohydrate content for meal announcements, potentially requiring less cognitive burden than quantifying carbohydrate content with each meal. Scrupulous diabetes self-management practices are particularly difficult to execute in childhood, adolescence, and emerging adulthood, all of which share a commonality of being developmental periods marked by dramatic cognitive, emotional, and physiological changes.

Even a small reduction in the burden of meal bolusing and correction bolusing, necessary self-management behaviors that are repeated multiple times per day, could be of tremendous benefit to youth and adolescents during these challenging periods. Technology acceptance models[14,15] consistently indicate the importance of perceived usefulness of a device as well as the ease of use being important for adaptation. This is the first study reporting improvement in glycemic control with youth using an AID system that eliminates the calculation of carbohydrate intake, basal insulin adjustments, and hyperglycemia corrections. Further studies will elucidate whether it is possible that these potential reductions in cognitive burden may lead to improved quality-of-life outcomes or to sustainability of using the system long term.

In this trial, the largest reduction in HbA1c occurred in participants who had the highest baseline HbA1c levels. This is a crucial finding, with the potential for substantial public health impact, since these young individuals with high HbA1c levels are at greatest risk for developing chronic diabetic microvascular and macrovascular complications, especially with a lifetime of diabetes pathophysiology ahead of them.[16,17] Historically, individuals with HbA1c >10% have often been excluded from clinical trials of new technology due to safety concerns; however, there was no upper limit for baseline HbA1c in this study.

Table 4. Efficacy Outcomes for Participants with Baseline HbA1c ≥9.0%

	Baseline		*Follow-up (at or over 13 weeks)*		*Adjusted difference BP minus SC (95% CI)*[b]	P[b]
	BP group (n = 27)[a]	*SC group (n = 7)*[a]	*BP group (n = 27)*[a]	*SC group (n = 7)*[a]		
Overall						
HbA1c (%), mean ± SD	9.7 ± 0.8	9.7 ± 0.5	7.9 ± 0.6	9.8 ± 0.8	−2.1 (−2.7 to −1.4)	<0.001
Mean glucose (mg/dL), mean ± SD	241 ± 32	257 ± 33	182 ± 12	247 ± 18	−64 (−75 to −53)	<0.001
Time 70–180 mg/dL, mean ± SD	28% ± 11%	22% ± 10%	56% ± 6%	25% ± 5%	31% (26% to 37%)	<0.001
Time >180 mg/dL, mean ± SD	71% ± 11%	76% ± 11%	43% ± 6%	74% ± 5%	−32% (−37% to −26%)	<0.001
Time >250 mg/dL, median (IQR)	43.1% (32.5%, 52.4%)	54.8% (34.0%, 63.8%)	15.9% (12.6%, 21.2%)	46.9% (44.6%, 54.7%)	−30% (−36.1% to −25.0%)	<0.001
Time <70 mg/dL, median (IQR)	0.5% (0.0%, 1.3%)	0.8% (0.1%, 3.3%)	1.6% (0.9%, 2.4%)	1.4% (0.6%, 1.8%)	0.7% (0.2% to 1.4%)	0.02
Time <54 mg/dL, median (IQR)	0.07% (0.00%, 0.30%)	0.10% (0.00%, 0.84%)	0.32% (0.16%, 0.51%)	0.15% (0.04%, 0.54%)	0.13% (−0.04% to 0.32%)	0.11
SD (mg/dL), mean ± SD	86 ± 14	90 ± 12	73 ± 10	91 ± 9	−15 (−23 to −8)	<0.001
Coefficient of variation (%), mean ± SD	36% ± 6%	35% ± 5%	40% ± 4%	37% ± 3%	3.1% (0.7% to 5.4%)	0.01

[a]One BP participant and one SC participant missing 13-week HbA1c. Median amount of CGM data for analyses were 318 (IQR 299–336) hours at baseline and 1909 (IQR 1745–1981) during follow-up in the BP group and 336 (IQR 320–336) and 1976 (IQR 1695–2090), respectively, in the SC group.

[b]All statistical testing is for superiority. *P*-values and 95% CIs are from mixed-effect models adjusting for baseline value of the metric, age at randomization, and site (random effect). Missing data were handled using direct likelihood analyses. Due to a skewed distribution, % time >250, <70, and <54 mg/dL were transformed using a rank normal transformation. Multiple comparisons were adjusted using the Benjamini-Hochberg adaptive false discovery rate correction procedure. This analysis was post hoc.

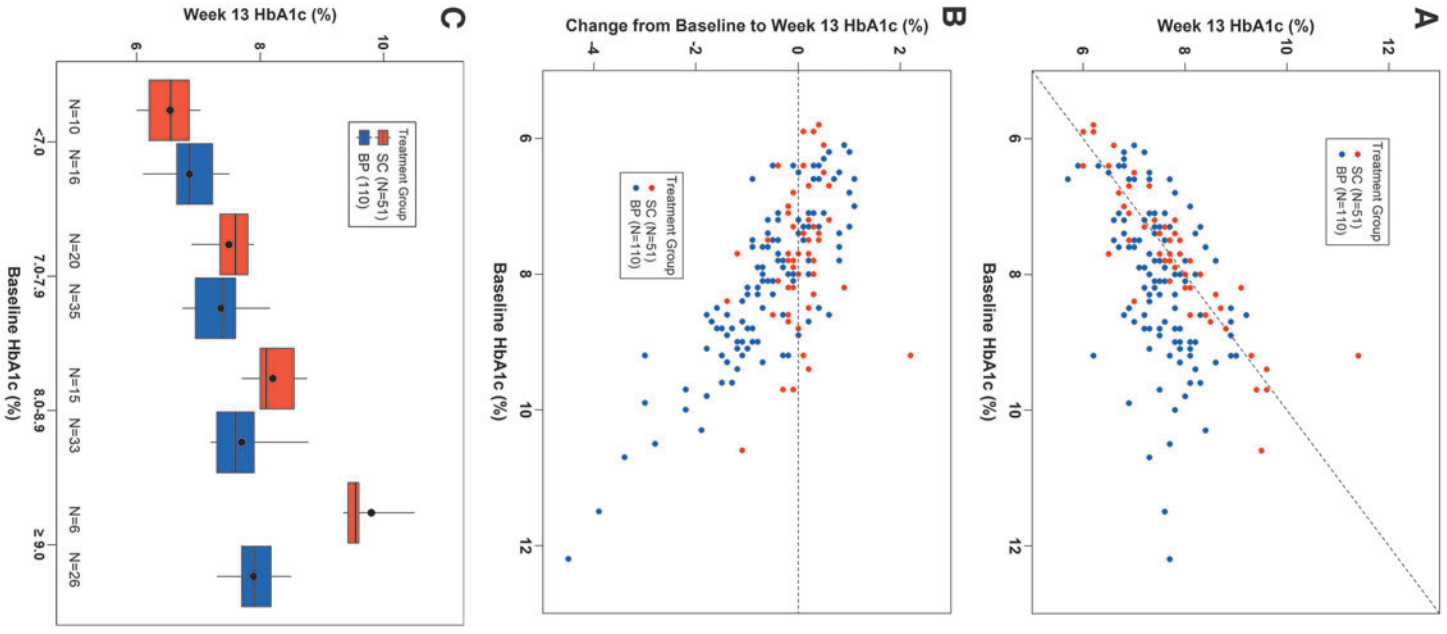

FIG. 1. HbA1c at 13 weeks. **(A)** A scatter plot of 13-week HbA1c versus baseline HbA1c with line of identity. **(B)** A scatter plot of change in HbA1c from baseline to 13 weeks versus baseline HbA1c, with the horizontal line representing zero change. **(C)** Box plots of 13-week HbA1c in subgroups based on baseline HbA1c. Black dots indicate the mean values, horizontal bars in the boxes indicate the medians, the bottom and top of each box represent the 25th and 75th percentiles, respectively, and the bottom and top whiskers represent the 10th and 90th percentiles, respectively.

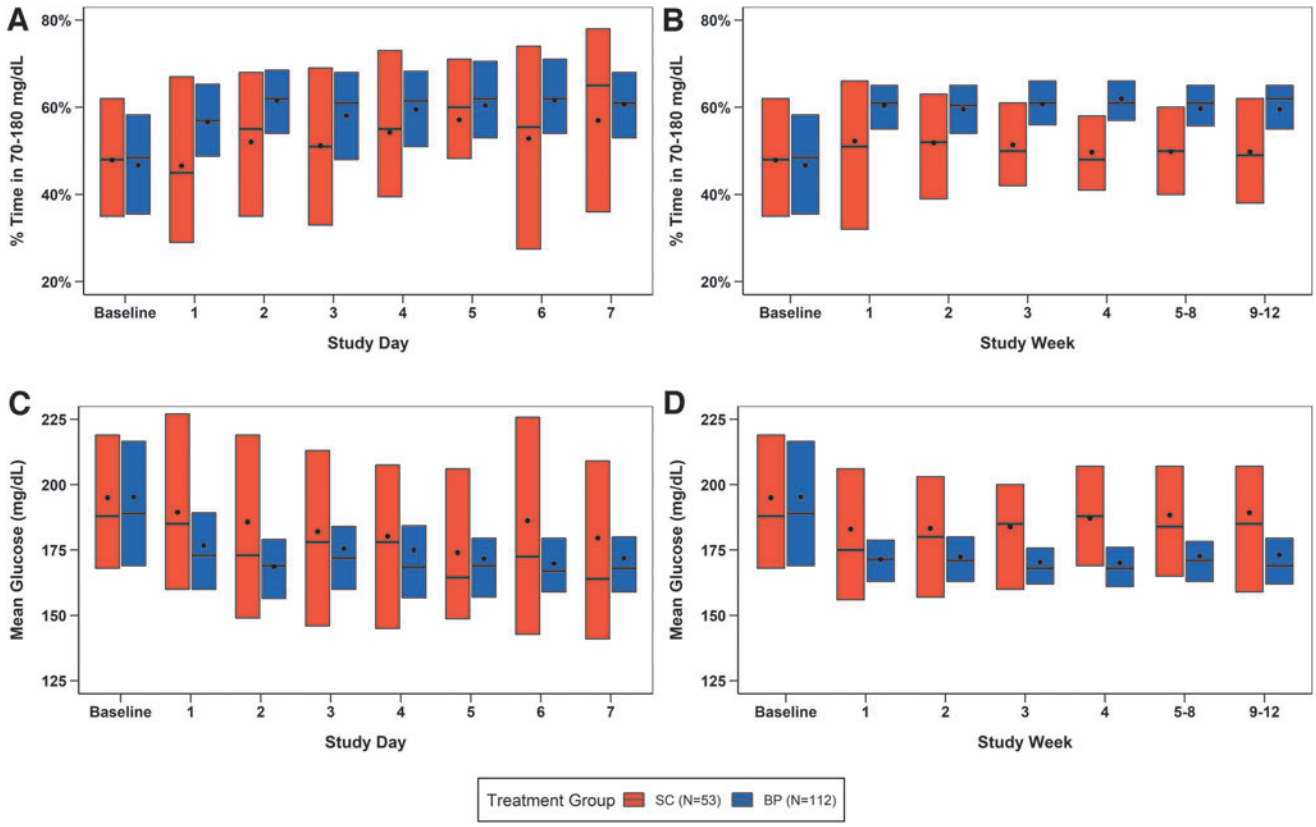

FIG. 2. TIR 70–180 mg/dL and mean glucose over first 7 days of BP use and over 13 weeks of trial. **(A, B)** TIR data and **(C, D)** mean glucose data for each day during the first 7 days of BP use and then in weekly intervals. Black dots indicate the mean values, horizontal bars in the boxes indicate the medians, and the bottom and top of each box represent the 25th and 75th percentiles, respectively. BP, bionic pancreas; SC, standard care; TIR, time in range.

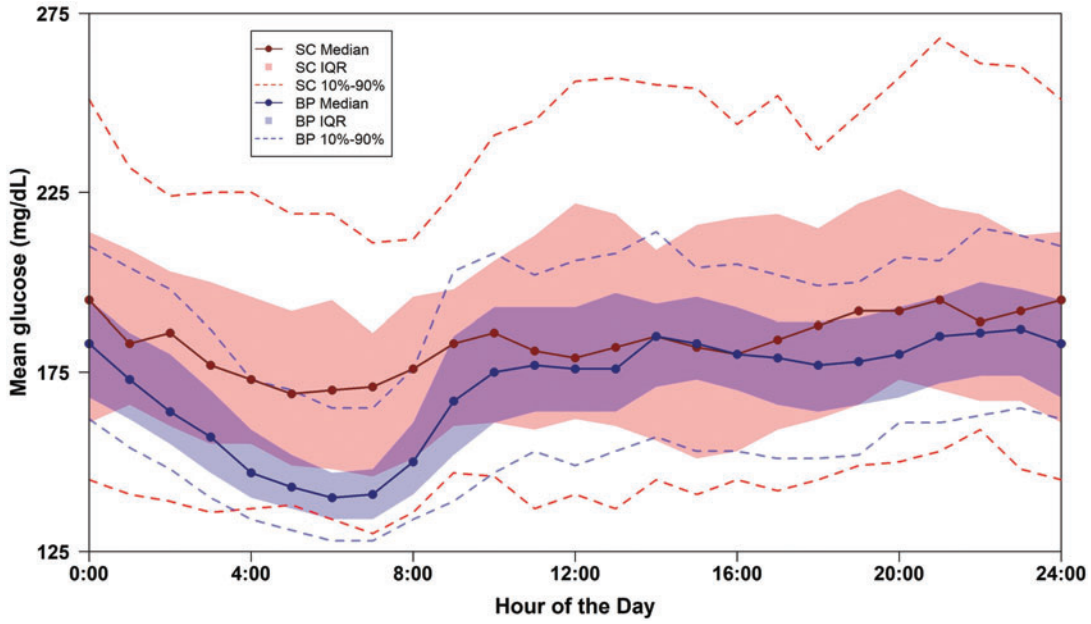

FIG. 3. Mean glucose by hour of the day over 13 weeks. Dots represent the median mean glucose. The shaded area represents the IQR and dashed curves represent the 10th and 90th percentiles over each hour of the day. BP, bionic pancreas; SC, standard care; IQR, interquartile range.

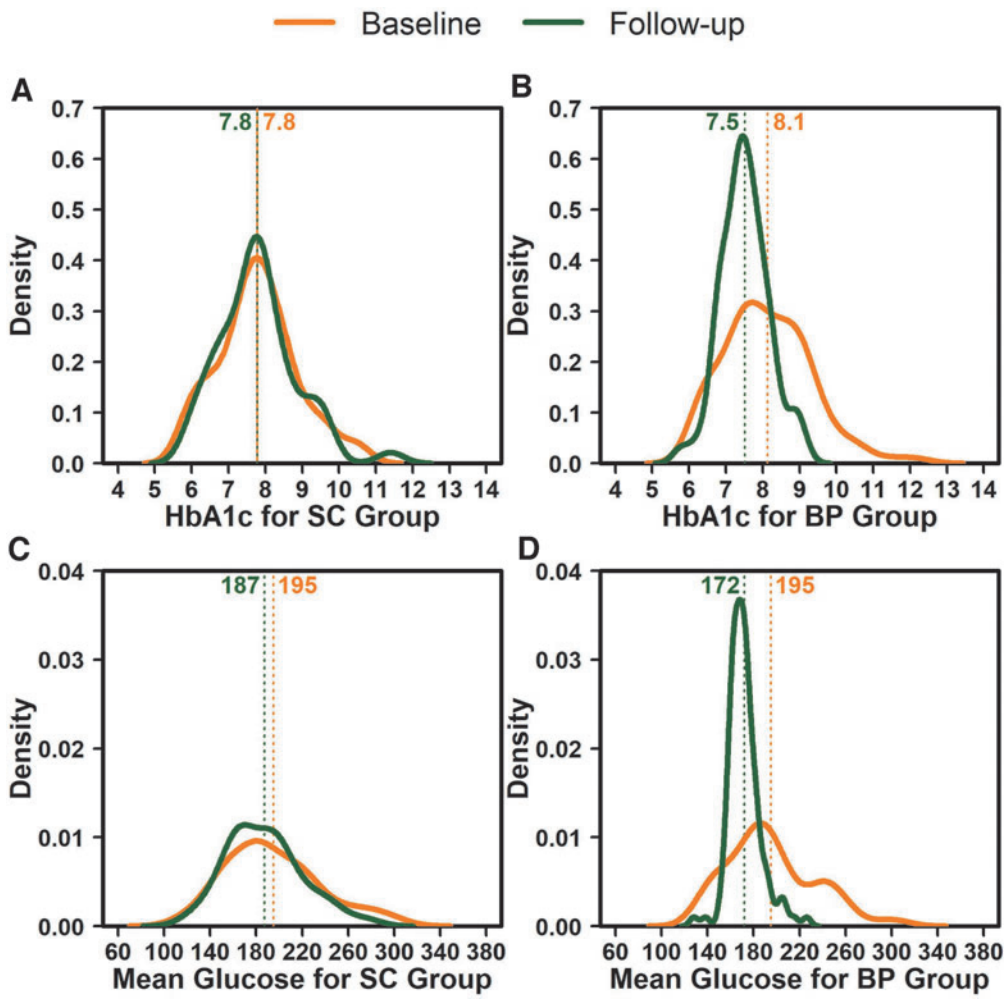

FIG. 4. Distribution of HbA1c and mean glucose at baseline and outcome for the BP and SC groups. **(A, B)** The HbA1c data for baseline and 13 weeks for the SC group and BP group, respectively. **(C, D)** Mean glucose measured with CGM over 13 weeks for the SC group and BP group, respectively. The curves represent the distribution of values at baseline and outcome. The dotted lines represent the mean values that are indicated numerically at the top of each line. BP, bionic pancreas; SC, standard care; CGM, continuous glucose monitoring.

We found that participants with high HbA1c levels not only used BP safely but also achieved dramatic improvements in glycemic control. A beneficial treatment effect was consistently observed across a wide range of other baseline characteristics, including participants of racial/ethnic minority groups or lower parental education or income, as well as in both MDI and pump users without automation. As anticipated, there was little further improvement observed in glycemia and CGM outcomes in participants using an HCL system before the study.

Randomized controlled trials of HCL systems have likewise shown improvement in HbA1c and/or CGM outcomes for children and adolescents. Breton et al.[6] reported a statistically significant 11% improvement in TIR and a nominal, although not statistically significant, 0.4% improvement in HbA1c over 16 weeks in youth 6–13 years of age using the Control-IQ system. Ware and colleagues[18] reported a 0.32% drop in HbA1c and 6.7% increase in TIR after 6 months using the Cambridge closed-loop algorithm in 6–18-year olds. In our study, participants using BP demonstrated a 0.5% drop in HbA1c and a 10% improvement in TIR over 13 weeks.

While the absolute outcomes of these three randomized controlled trials cannot be directly compared due to different participant baseline characteristics, study designs, and study durations, it is notable that equivalent and sometimes superior improvement in glycemic outcomes were observed with BP, despite no carbohydrate quantification for meal boluses, no setting or adjusting basal insulin delivery, and no user-initiated correction boluses.

With respect to safety, there were few severe hypoglycemia events and no diabetic ketoacidosis events in this pediatric cohort. The most frequently reported adverse event in the BP group was hyperglycemia with or without ketosis, often attributed to infusion set failure. According to the protocol, infusion set failures were only reportable adverse events in BP groups. Therefore, none were reported in the SC group. In addition, the difference between groups likely was influenced by BP participants receiving system-specific instructions on identifying, managing, and reporting potential infusion set failures, whereas the SC group was instructed to contact their personal HCP for any problem and not the study staff. Another difference was that the BP group was unable to administer and observe the

Table 5. Adverse Events and Safety Outcomes

	BP (n = 112 randomized)	*SC (n = 53 randomized)*	P
All reportable AEs, N events	181	4	
Number of AEs per participant, *n* (%)			
0	29 (26)	50 (94)	
1	32 (29)	2 (4)	
2	26 (23)	1 (2)	
3	15 (13)	0 (0)	
4	4 (4)	0 (0)	
5	3 (3)	0 (0)	
6	2 (2)	0 (0)	
7	0 (0)	0 (0)	
8	0 (0)	0 (0)	
9	1 (<1)	0 (0)	
Severe hypoglycemic events [a]			
Number of SH events per participant, *n* (%)			
0	109 (97)	52 (98)	
1	3 (3)	1 (2)	
Incidence rate per 100 person-years	10.4	7.3	
Diabetic ketoacidosis events [b]			
Number of DKA events per participant, *n* (%)			
0	112 (100)	53 (100)	
Other SAEs[c]			
Number of SAEs per participant, *n* (%)			
0	110 (98)	52 (98)	
1	2 (2)	1 (2)	
Incidence rate per 100 person-years	6.9	7.3	
Participants with worsening of HbA1c from baseline to 13 weeks by >0.5%, *n* (%)	13 (12)	4 (8)	0.27[d]
Other AEs, N events/N participants			
Hyperglycemia with or without ketosis related to study device[e]	126/68	NA	
Hyperglycemia with or without ketosis not related to study device	41/32	0/0	
Nonsevere hypoglycemia	1/1	0/0	
Other reportable AEs	8/7	2/1	

[a]A severe hypoglycemic event is defined as a hypoglycemic event that (1) required assistance of another person due to altered consciousness and (2) required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. The analysis plan specified that statistical testing would only be done if five or more events in total between groups occurred.

[b]A hyperglycemic event is classified as DKA if the following are present: (1) symptoms such as polyuria, polydipsia, nausea, or vomiting; (2) serum ketones >1.5 mmol/L or large/moderate urine ketones; (3) either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and (4) treatment provided in a health care facility.

[c]Self-harm attempts (2) in BP group and primary spontaneous pneumothorax (1) in SC group.

[d]*P*-value produced from a logistic regression model adjusting for age at randomization, central lab HbA1c at randomization, and site (random effect).

[e]Of the 126 hyperglycemia events related to the iLet, 103 were due to an infusion set issue, 7 to cartridge issues, 6 to user errors, 5 to battery charging issues, 2 to iLet algorithm issues, 1 to CGM issue, 1 to motor issue, and 1 to iLet screen issue.

AEs, adverse events; NA, not applicable; SAEs, serious adverse events.

effect of a manually programmed correction dose on CGM glucose levels to help assess for an infusion site failure.

The frequency of infusion set failures may have also been impacted by participants having only one type of infusion set to use with BP (a commonly used, commercially available 6 mm Teflon set with a 90-degree insertion), whereas, in clinical practice, insulin pump users are able to choose from among a variety of infusion sets that are straight or angled, are of different lengths, and are made of either Teflon or steel. Having a choice of infusion sets may be particularly important for youth to accommodate the challenges related to athletics, and other activities.

Assuming that infusion sets were changed on average every 3 days per participant instructions, the 103 hyperglycemia adverse events associated with infusion set failures in the BP group represent a failure rate of 3.0% for 3420 infusion sets. This observed rate of infusion set failures with associated hyperglycemia may not be higher than the failure rate that occurs with other insulin pumps and infusion sets. Kanapka et al.[19] analyzed data from two HCL trials using tubed infusion sets and reported that infusion set replacement occurred following a period of prolonged hyperglycemia (glucose level >300 mg/dL at the time of removal and for at least 90 out of the prior 120 min) within 3 days of insertion in 5.8% of 4428 infusion sets in 14–17-year olds and in 4.4% of 5745 infusion sets in 6–13-year olds.

Other studies conducted specifically to evaluate infusion set failures have reported failure rates associated with hyperglycemia of 4.6%–15% within 3 days.[20–22] Our experience in this trial, supported by these prior studies, indicates

that the infusion set remains a weak link in all insulin pump systems, including advanced insulin delivery systems such as BP. Diabetes clinicians must emphasize this enduring mechanical risk for users of all insulin pump systems, reinforcing the importance of surveillance, essential ketone monitoring, and frequent infusion set changes with persisting hyperglycemia.

A strength of this trial is the inclusion of participants who, before the study, were using a HCL system, a pump without automation, or MDI for insulin delivery, and had wide range of levels of glycemic control, with baseline HbA1c values ranging from 5.8% to 12.2%. Furthermore, the cohort was racially and socioeconomically diverse, which has been highlighted as a moral imperative for clinical trials,[23] increasing the generalizability of the results to the population at large. In addition to the baseline characteristics, the inclusiveness of HCL systems in the SC arm and requiring CGM for all participants indicate that the trial results are not due to a contrived comparison with outdated technologies.

Furthermore, the participant retention rate in both arms was 100%, with high adherence to use of assigned devices in both treatment groups. The main limitations of the trial are that the trial duration was only 13 weeks and that the low amount of baseline hypoglycemia precluded an evaluation as to whether the insulin-only BP system can reduce hypoglycemia, but it was clear from the results that it does not increase hypoglycemia.

In conclusion, BP using insulin aspart or insulin lispro substantially improve HbA1c and CGM metrics of TIR, mean glucose, and hyperglycemia, without increasing hypoglycemia, in comparison with standard care insulin delivery plus CGM in youth with T1D. The trial included a more diverse population than prior studies of HCL systems with respect to minority representation, method of insulin delivery, and baseline HbA1c levels.

The improvement in HbA1c with BP was large for participants with baseline HbA1c levels ≥9.0% and even 10.0%, indicating that this group should not be excluded from future access to the BP system. The BP differs from the current FDA-approved/cleared HCL systems in not requiring any information about the previous insulin regimen, and not requiring carbohydrate counting at mealtimes or correction boluses to treat hyperglycemia. This reduced user interaction compared to current HCL systems may facilitate adoption of AID by a wider spectrum of youth with T1D and a broad spectrum of HCPs.

Authors' Contributions

L.H.M.: conceptualization, methodology, investigation, and writing—original draft. B.A.B.: investigation, project administration, and writing—review and editing. F.C.: investigation, project administration, and writing—review and editing. M.D.: investigation, project administration, and writing—review and editing. G.F.: investigation, project administration, and writing—review and editing. R.Z.J.: investigation, project administration, and writing—review and editing. N.M.: investigation, project administration, and writing—review and editing. A.M.: investigation, project administration, and writing—review and editing. R.P.W.: investigation, project administration, and writing—review and editing. P.C.W.: investigation, project administration, and writing—review and editing. S.J.R.: conceptualization, investigation, project administration, and writing—review and editing. E.R.D.: conceptualization, investigation, project administration, and writing—review and editing. F.H.E.: conceptualization, investigation, project administration, and writing—review and editing. K.J.R.: methodology, data curation, resources, and writing—review and editing. C.A.B.: investigation, project administration, and writing—review and editing. Z.L.: formal analysis, validation, and writing—original draft. M.C.M.: formal analysis, validation, and writing—original draft. P.C.: formal analysis, validation, and writing—original draft.

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Author Disclosure Statement

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Supplementary Material

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